Contractile force generation by 3D hiPSC-derived cardiac tissues is enhanced by rapid establishment of cellular interconnection in matrix with muscle-mimicking stiffness.

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Public Summary:
Coronary heart disease and the associated myocardial infarction are the leading causes of death in the US and globally. In 2013, coronary heart disease alone caused ~1 of every 7 deaths in the US. Following the damage to myocardium, human heart exhibits deficient ability to restore its function due to limited self-renewal capacity of adult cardiomyocytes (CMs). Current treatment modalities for loss of heart function include supplementation of therapeutic products, surgical reconstruction, implantable devices, or ultimately organ transplantation. Although these conventional treatments have shown some efficacy and improved the quality of life for the patients, they cannot effectively regenerate the damaged heart tissue and restore its function. Clinical trials of cell transplantation have shown promise to replace the dead cells and restore the impaired function of heart. However, the efficacy of cell transplantation has been controversial mainly due to poor cell viability, retention, and engraftment. Therefore, it is crucial to develop more reliable and reproducible methods to deliver therapeutic cells. Here, we demonstrate bioengineering of human cardiac microtissues using chemically-crosslinked gelatin hydrogels with enhanced stiffness and tunable degradation properties, obtained by functionalizing the gelatin polymer with different degrees of vinyl sulfone (VS) groups. The effects of varying hydrogel stiffness and degradation on cardiac tissue formation by hiPSC-CMs were evaluated by encapsulating cells at physiologically-relevant density (125 M cells/mL). Outcomes were evaluated by characterizing cell survival as well as structural organization and contractile function of newly formed cardiac tissues.

Scientific Abstract:
Engineering 3D human cardiac tissues is of great importance for therapeutic and pharmaceutical applications. As cardiac tissue substitutes, extracellular matrix-derived hydrogels have been widely explored. However, they exhibit premature degradation and their stiffness is often orders of magnitude lower than that of native cardiac tissue. There are no reports on establishing interconnected cardiomyocytes in 3D hydrogels at physiologically-relevant cell density and matrix stiffness. Here we bioengineer human cardiac microtissues by encapsulating human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) in chemically-crosslinked gelatin hydrogels (1.25 x 108/mL) with tunable stiffness and degradation. In comparison to the cells in high stiffness (16 kPa)/slow degrading hydrogels, hiPSC-CMs in low stiffness (2 kPa)/fast degrading and intermediate stiffness (9 kPa)/intermediate degrading hydrogels exhibit increased intercellular network formation, alpha-actinin and connexin-43 expression, and contraction velocity. Only the 9 kPa microtissues exhibit organized sarcomeric structure and significantly increased contractile stress. This demonstrates that muscle-mimicking stiffness together with robust cellular interconnection contributes to enhancement in sarcomeric organization and contractile function of the engineered cardiac tissue. This study highlights the importance of intercellular connectivity, physiologically-relevant cell density, and matrix stiffness to best support 3D cardiac tissue engineering.

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